NÖRO PSİKİYATRİ ARŞİVİ

Invited Editorial

Arch Neuropsychiatry 2016; 53: 192-193 • DOI: 10.5152/npa.2016.01082016

Nonconvulsive Status Epilepticus: An Intriguing, Highly Heterogeneous Neuropsychiatric Condition with Blurring Clinical Margins, Sharpening EEG Criteria and Still Unsolved Background

Betül BAYKAN

Department of Neurology, Division of Clinic Neurophysiology, İstanbul University İstanbul School of Medicine, İstanbul, Turkey

Even though nonconvulsive status epilepticus (NCSE) always evokes great interest among the neuropsychiatric community, its mysteries remain still uncovered despite remarkable advances in neuroscience. Due to the marked heterogeneity in clinical features and lack of a uniform diagnostic clue, its diagnosis largely depends on clinical awareness and high rates of suspicion to order an EEG. This editorial will focus on several areas of NCSE shortly, with comments on some recent work and developments in the field.

Long-lasting epileptic state without convulsions was first noted in the 19th century without any EEG correlate available under many different names like epileptic fugue, ecstasy, delirium or even mania. But it was not possible to differentiate these NCSE-like descriptions from encephalopathies or psychiatric conditions in old texts without an EEG proof. Therefore, we currently do not exactly know who had first described NCSE, among the names like Charcot, Prichard. The first clinical and EEG description of a patient who had hypoglycemia was reported by Lennox in 1945 (1). After definitions of focal and generalized NCSE forms, accumulating knowledge and technical advances caused a widening of the NCSE term to include many different entities resulting in different debates currently.

It is difficult to estimate the exact incidence of NCSE due to the differences in definition of NCSE, diagnostic difficulties and varying characteristics of study groups like age etc. The estimated figures are around 1.5-18.3/100000 per year. NCSE prevalence is about 8-27% in patients with coma admitted to intensive care units, where the mortality and outcome depends on the etiology (1). The wide clinical spectrum including walking patients with attention deficits or with psychiatric symptoms only, or those already have been diagnosed with epilepsy in one end and patients with anoxia-related coma with high mortality rates in the other end poses important difficulties, understandably (2).

There is no single illness called NCSE and indeed, there are no largely accepted definition and classification on this issue. One of the most notable recent developments in the field is the new status epilepticus classification of ILAE (International League against Epilepsy), that hopefully will facilitate the research on NCSE and provide standardization (3). This text defined two different time points with operational dimensions, hypothetically: t1 is the time point needed to say that a seizure is abnormally prolonged (where urgent treatment is indicated) and t2 emphasizes long lasting consequences, like neuronal damage, death and network reorganization may occur. Regarding the NCSE subtypes, without any clear evidence, t1 is reported as 10 minutes and t2 is >60 min for focal NCSE with loss of consciousness, whereas t1 is determined as 10-15 min and t2 is underlined as unknown for absence status epilepticus, the generalized form of NCSE. Another new feature in this classification is the proposal of a frame with 4 axes in line with clinical diagnosis, research and management issues. These axes are proposed as 1) semiology, 2) etiology, 3) EEG correlates and 4) age (3). The table shows the subtypes of NCSE with the present style in the latest classification.

Moreover, this new classification approaches to some clinical entities as borderline syndromes due to their current undetermined and doubtful relations with NCSE. Epileptic encephalopathies, coma with epileptiform EEG patterns without any evolution (periodic lateralized epileptiform discharges and generalized periodic epileptiform discharges with monotonous appearance), behavioral disturbances in epileptic individuals (for example psychosis) and epileptiform EEG patterns in relation with acute confusional episodes are among these borderland pictures. Aphasic status in Landau-Kleffner syndrome, absence status in juvenile absence epilepsy, NCSE in Creutzfeldt-Jakob disease and de novo (sometimes recurring) absence status of elderly are other entities listed deserving special attention (2,3).

The patients with recurrent absence status attacks as the determining feature and main seizure type in terms of an atypical picture not fitting to the known syndromes in the classification, during the course of chronic idiopathic/genetic generalized epilepsy were described by us for the first time, more than a decade ago (4). Afterwards, Genton et al. (5) also emphasized that there is an epilepsy form with recurrent absence status attacks in another study describing similar patients, supported our results by recommending the name of "absence status epilepsy" and indicated that this picture is a different syndrome. Absence status epilepticus has been known to have a good prognosis and responds rapidly to IV treatment. The genetic and pathophysiological backgrounds of this interesting picture have not been illuminated yet, but it seems a good

Correspondence Address: Betül Baykan, İstanbul Üniversitesi İstanbul Tıp Fakültesi, Nöroloji Anabilim Dalı, Klinik Nörofizyoloji Bilim Dalı, İstanbul, Türkiye E-mail: betulbaykan@yahoo.com

Received: 27.07.2016 **Accepted:** 01.08.2016

Table 1. Non-convulsive status epilepticus subtypes in the last classification (3)

(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
B.2.a. Generalized
B.2.a.a Typical absence status
B.2.a.b Atypical absence status
B.2.a.c Myoclonic absence status
B.2.b. Focal
B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/ experiential, or auditory symptoms)
B.2.b.b Aphasic status
B.2.b.c With impaired consciousness
B.2.c Unknown whether focal or generalized
B.2.c.a Autonomic SE (Panayiotopoulos syndrome)

model for NCSE investigations due to recurrences. It is tempting to speculate that some mechanisms related to the functions that normally serve in termination of seizures and related neuronal networks are in charge.

Despite the enormous developments in neuro-genetics research, the susceptibility genes for NCSE or for status epilepticus in general could not be uncovered yet. NCSE is rather frequently encountered in various genetic etiologies like ring 20 chromosome and other caryotype abnormalities, Angelman syndrome, Dravet syndrome, some hereditary metabolic diseases, mitochondrial disorders or in malformations of cortical development (2,3).

Similarly, the recent important developments in neuro-imaging do not show sounding reflections for NCSE at the moment, but we could rather easily detect the etiology and underlying localizations of focal NCSE forms, which were not known in the past with the help of advanced MRI techniques and PET/SPECT imaging (1). Currently, there is a scant of information in NCSE literature with no controlled large multimodal neuroimaging series due to some reasonable explanations like the need for emergency treatment, waiting until the picture is controlled and additional medical problems restricting the imaging time and use of contrast agents. Diffusion weighted and FLAIR sequences are especially useful to show the severity of early neuronal impairment and its distribution and repeated MRI investigations are recommended. A handful of studies in NCSE patients demonstrated regional hyperintensity in DWI and restriction in ADC maps, besides involvement of cortical areas, hippocampus and pulvinar (1).

Various CNS disorders including stroke with the highest frequency, conditions related to epilepsy and its treatment, toxic and metabolic problems, systemic and critical disorders and many drugs especially the psychiatric drugs may trigger NCSE attacks; detailed knowledge on these issues is out of the scope of this paper and is reported in two books; the first one of them being in Turkish besides many current reviews (1,2). One of the frequent and important triggers currently encountered is cephalosporin treatment in patients with renal failure and infections (6). This picture cannot be successfully controlled unless the antibiotic treatment is withdrawn or changed. Furthermore, NCSE related to neuronal auto-antibodies is very recently recognized and deserves special attention because this picture may imitate psychiatric disorders and cannot be treated with antiepileptic drugs but improves after immune treatments (7).

Besides the widening and blurring clinical spectrum of NCSE, there are diagnostic problems and question marks during interpreting the EEG findings, even for EEG specialists especially in cases who admitted to intensive care units and in some special situations like epileptic encephalopathies and other pictures already bearing very active epileptiform EEG patterns with subtle clinical features. Therefore, international meetings were organized and "Salzburg Consensus Criteria" with strictly different forms in cases with or without epileptic encephalopathy were developed. The frequency of epileptic discharges (more or less than 2.5 Hz), rhythmic delta/theta waves with clinical and EEG response to IV anti-epileptic drugs and typical spatio-temporal evolution patterns of seizure activity were also taken into consideration in these new criteria, which hopefully will help in correct diagnosis (8).

Another group of patients with frequent NCSE with special diagnostic, etiologic and management difficulties is the elderly patients with critical illnesses. There are ongoing debates whether continuous EEG monitorization is needed in every patient admitted to intensive care units and how aggressive should they be treated in case of diagnosis of NCSE, due to known fact that aggressive anti-epileptic treatment might be harmful (9). A good perspective on the treatment issues of NCSE should clearly note that treatment, just as diagnosis, must be tailored to the individual type and etiology of NCSE.

In conclusion, NCSE should be well-recognized with its wide clinical margins and always be kept in mind in the differential diagnosis of many neurologic and psychiatric conditions. The NCSE cases should be evaluated according to their clinical status, EEG findings and criteria for the diagnosis should be interpreted with wisdom by experts. Moreover, the etiology and associated conditions should be investigated with caution. There is still a need for further investigations regarding to its mechanisms, definition, diagnostic criteria and optimal management options and those patients with coma and critical illnesses and those with real epileptic mechanisms should be differentiated. At the current state of art, we should first appropriately diagnose, follow-up and investigate NCSE patients carefully and manage their rational treatment according to the rule "primum nil nocere".

REFERENCES

1. Kaplan PW, Drislane FW. Nonconvulsive Status Epilepticus. DemosMedical Publishing, 2009; New York.
2. Baykal B. Nonkonvülzif status epilepticus. Artpres, 2004, İstanbul.
3. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015 ;56:1515-1523. [CrossRef]
4. Baykan B, Gokyigit C, Gurses C, Eraksoy M. Recurrent absence status epilepticus: clinical and EEG characteristics. Seizure 2002; 11:310-319. [CrossRef]
5. Genton P, Ferlazzo E, Thomas P. Absence status epilepsy: delineation of a distinct idiopathic generalized epilepsy syndrome. Epilepsia 2008; 49:642-649. [CrossRef]
6. Öztürk S, Kocabay G, Topçular B, Yazıcı H, Çağatay AA, Bahat G, Baykan B, Türkmen A, Yıldız A. Non-convulsive status epilepticus following antibiotic therapy as a cause of unexplained loss of consciousness in patients with renal failure. Clin Exp Nephrol 2009; 13:138-144. [CrossRef]
7. Çikrikçili U, Ulusoy C, Turan S, Yıldız Ş, Bilgiç B, Hanagasi H, Baykan B, Tüzün E, Gürvit H. Non-convulsive status epilepticus associated with glutamic acid decarboxylase antibody Clin EEG. Neurosci 2013; 44:232-236.
8. Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, Brøgger JC, Trinka E. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013; 54(Suppl 6):28-29.
9. Altindag E, Okudan ZV, Tavukçu Özkan S, Krespi Y, Baykan B. Electroencephalographic patterns recorded by continuous video-EEG monitoring in the critically ill patients with altered mental status. Arch Neuropsychiatry. Accepted DOI: 10.5152/npa.2016.14822 [CrossRef]